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Systematic Review

Impact of Irradiation on the Adhesive Performance of Resin-Based Dental Biomaterials: A Systematic Review of Laboratory Studies

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Abstract: Head and neck cancers are a significant global health burden, with radiation therapy being a frequently utilized treatment. The aim of this systematic review was to provide a critical appraisal of laboratory studies that assessed the effect of irradiation on the adhesive performance of resin-based biomaterials. The analysis included 23 laboratory studies obtained from five databases, with most studies using human enamel, dentin, or both, and bonding procedures involving the fabrication of direct restorations, standardized specimens, bonding of orthodontic brackets, and luting of endodontic fiber posts. The protocols used for irradiation varied, with most studies exposing specimens made from extracted teeth to irradiation using cabinet irradiators to simulate treatment of head and neck cancer. The findings indicate that irradiation reduces the bond strength of dental adhesives and resin-based composites on flat, ground enamel and dentin specimens, with different adhesives and timing of irradiation having a significant impact on adhesive performance. Irradiation also increased microleakage in most studies. The effect of irradiation on marginal adaptation of direct resin-based composite restorations was inconclusive. This systematic review indicates that irradiation has detrimental effects on the adhesive performance of resin-based biomaterials and highlights the need for further clinical and laboratory studies evaluating the performance of adhesive materials and approaches to improve it.

Keywords: dental materials; dental bonding; permanent dental restoration; head and neck neoplasms; radiotherapy; radiation oncology

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1. Introduction

Head and neck cancers pose a significant global health burden, accounting for approximately 5.7% of all cancer-related deaths worldwide [1,2]. Treatment options for head and neck cancers vary depending on the diagnosis and stage of the disease. Radiation therapy is a frequently utilized treatment for head and neck cancers, either as a standalone option or in conjunction with chemotherapy, surgical intervention, or both [3–7].

Between 30% and 40% of patients with head and neck cancer are diagnosed with stage I or II disease, which can often be effectively treated with either surgery alone or definitive radiation therapy alone [5]. Over 60% of head and neck squamous-cell cancer cases are diagnosed at stage III or IV, indicating large tumors with marked local invasion, regional node metastases, or both [5]. Treatment decisions in such cases depend on primary cancer size, location, disease stage, age, patient preferences, performance status, and coexisting conditions [5]. Surgical resection with elective neck dissection is preferred for oral cavity cancer, followed by adjuvant radiotherapy or chemoradiotherapy [5].

However, despite its efficacy, radiation therapy has significant toxicity with both acute and late side-effects. Acute side-effects of radiation therapy include mucositis, xerostomia, dysphagia, and taste disturbance or loss [8]. Late side-effects of radiation therapy can occur months or even years after treatment has ended. These can include radiation-induced fibrosis and radiation-related caries [8].

Radiation-related caries occur in approximately 29% of patients within 3 months of completing treatment [9,10]. This susceptibility to caries is largely due to changes in saliva quantity and quality, as well as direct radiation effects on enamel and dentin [11–14]. In addition, oral trismus and mucositis, common side-effects of radiation therapy, can lead to inadequate biofilm control and increased consumption of carbohydrate-rich foods, both contributing factors to radiation-related caries [8,10,15].

Patients with head and neck cancer who undergo radiation therapy require comprehensive dental care, with special measures needed for caries prevention and control [11,15–17]. Owing to the high incidence of radiation-related caries, restorative interventions are often necessary [10]. In recent years, there has been an increase in studies evaluating the impact of irradiation on enamel, dentin, and the adhesive performance dental biomaterials [12,18].

The adhesive performance of dental biomaterials refers to their ability to bond to tooth structure or other dental materials, creating a strong and durable bond. This performance is a critical factor in the success of many dental treatments, including orthodontic procedures and restoration of teeth with defects caused by caries, tooth wear, or dental injuries [19,20]. Dental biomaterials that exhibit excellent adhesive performance typically have a high bond strength, good retention, low microleakage, and minimal marginal gaps [20,21].

The purpose of this systematic review is to provide a critical appraisal of laboratory studies that assessed the effect of irradiation, performed to simulate head and neck cancer treatment, on the adhesive performance of resin-based biomaterials. By synthesizing the findings of these studies, this review aims to contribute to a better understanding of the impact of radiation therapy on dental biomaterials and to inform clinical decision making for the management of radiation-related dental complications.

2. Materials and Methods

2.1. Research Question

The protocol for this systematic review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO 2022, CRD42022384753). The systematic review, taking account of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, addressed the following question using the PICO (population, intervention, comparison, and outcome) framework [22]: In specimens made from or featuring enamel and/or dentin (human, bovine), how does irradiation simulating head and neck cancer treatment performed ahead of bonding or after bonding affect the adhesive performance of resin-based biomaterials compared with unirradiated controls?

2.2. Eligibility Criteria

Studies with full study reports were selected according to the inclusion and exclusion criteria given below. No time or language restrictions were applied.

2.3. Inclusion Criteria

- In vitro/laboratory study
- Use of pre-irradiation or post-irradiation bonding with a resin-based dental biomaterial (i.e., dental adhesives, resin-based composites, resin-based luting materials, resin-modified glass ionomer cements, compomers, resin-based sealants, and blocks made from resin-based composite for use in computer-aided design and computer-aided manufacturing)
- Data on adhesive performance in terms of bond strength, marginal discoloration, microleakage, marginal adaptation, debonding, or interfacial fracture toughness
- Specimens made from or featuring human or bovine enamel, dentin, or both

2.4. Exclusion Criteria

- In silico study
- Clinical study
- Animal study
- Case report
- Review article
- Study assessing laser irradiation as surface pretreatment
- Study assessing irradiation as disinfection method
- Poster
- Abstract-only paper

2.5. Search Strategy

Five databases, Cochrane Library, Embase, OpenGrey through DANS, PubMed, and Web of Science, were searched on 10 January 2023. The search strings, which were as similar as possible and tailored to the controlled vocabulary and syntax rules of each database, are included in the Supplementary Materials.

2.6. Selection Process

After removal of duplicates through manual review (J.D.H.), two investigators (F.E. and J.D.H.) independently screened the titles and abstracts of articles retrieved through the electronic search against the eligibility criteria and selected articles considered potentially relevant for this systematic review. During the screening, author names and journals were unblinded. After retrieving the full articles of potentially relevant studies, three investigators (F.E., F.K.M., and J.D.H.) independently assessed each study report according to the eligibility criteria. Discrepant judgments regarding study eligibility were resolved by consultation with a fourth investigator (J.M.A.). Reasons for exclusion were recorded.

2.7. Data Collection

Three investigators (F.E., F.K.M. and J.D.H.) independently extracted qualitative and quantitative data of included studies into pilot-tested, structured spreadsheets. A fourth investigator (J.M.A.) made a final decision in case of incongruous assessments. No unpublished data were sought from corresponding authors or other sources. Data were extracted for details of dental specimens assessed (enamel, dentin, or both; human, bovine, or both), number of specimens, specimen fabrication, specimen shape, sample grouping, irradiation protocol, adhesives and resin-based materials used, test methods used to assess adhesive performance, and main findings.

2.8. Risk-of-Bias Assessment

The risk of bias of included studies was assessed independently by three investigators (F.E., F.K.M., and J.D.H.) using the RoBDEMAT tool [23]. An individual RoBDEMAT was completed for each laboratory study included in the systematic review. A fourth investigator (J.M.A.) resolved any inconsistent appraisals.

3. Results

3.1. Included Studies

Figure 1 shows the results of the study selection process, which led to the inclusion of 23 laboratory studies, whose year of publication ranged from 2001 to 2023. Data extracted from the reports of these studies are reported in detail in Table A1. During full-text assessment, two studies were excluded because their study reports were available as abstract-only papers but not as full-text articles [24,25]. One study was excluded because irradiation was used as a method of disinfection of specimens [26]. One study contained no data on adhesive performance and was, therefore, excluded [27].

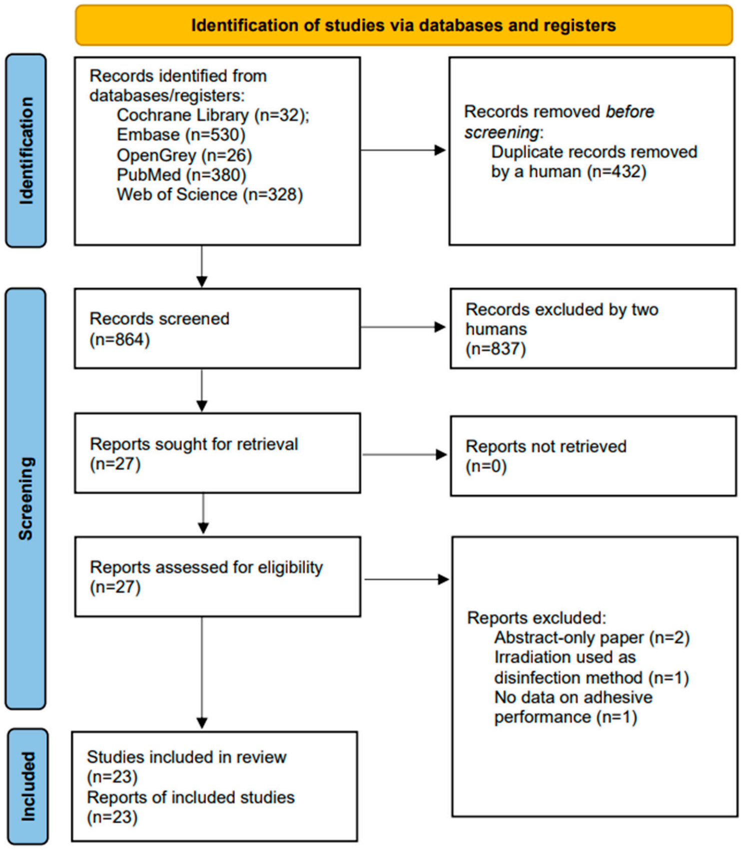

Figure 1. PRISMA 2020 flow diagram depicting the selection of records for this systematic review [22].

3.2. Characteristics of Included Studies

3.2.1. Dental Specimens

Most studies used human enamel, dentin, or both. One study used specimens made from bovine teeth [28]. Two studies used deciduous molars to fabricate specimens [29,30]. Extracted molars were used in most studies to provide the bonding substrate, with some studies furnishing no information whether the sample comprised permanent molars, deciduous molars, or both.

3.2.2. Bonding

The bonding procedures in the included studies comprised fabrication of direct restorations (Class I, II, and V), fabrication of standardized specimens with resin-based composite bonded on flat, ground enamel and/or dentin, bonding of orthodontic brackets, and luting of endodontic quartz fiber posts.

3.2.3. Irradiation Protocols

Two studies used extracted teeth that had been exposed to an irradiation dose of $\geq$50 Gy during radiation therapy prior to tooth removal [31,32]. Most studies used cabinet irradiators to expose specimens made from extracted teeth to high-energy X-ray radiation. A total dose level of 60 Gy, usually achieved through daily, fractional irradiation over 6 weeks, was most used in the included studies. To examine possible dose–effect relationships, two studies exposed different groups to different total dose levels, ranging from 10 Gy to 70 Gy [29,33]. The timepoint of irradiation differed across the included studies; the bonding procedures were performed before, during, or after irradiation of the specimens, with some studies subjecting different samples at different timepoints to irradiation in order to assess the impact of the timing on adhesive performance. Two studies included a comparison between samples restored immediately after irradiation or with a 6-month period in between [30,34]. One study evaluated the effect of covering restored and unrestored teeth with C-shaped shields made from 0.5 mm thick aluminum during irradiation [35].

3.2.4. Resin-Based Biomaterials

The adhesives used in the included studies comprised etch-and-rinse adhesives (two-step, three-step, and four-step), self-etch adhesives (one-step and two-step), and universal adhesives that were applied in self-etch or etch-and-rinse mode. One study assessed a resin-modified glass ionomer material in addition to resin-based composite [36]. Apart from the study that bonded quartz fiber posts in root canals using dual-curing resin-based luting material, most studies used light-curing resin-based composites to create standardized restorations or cylinders for bond strength testing and other assessments of adhesive performance.

3.2.5. Methods to Evaluate Adhesive Performance

The methods employed to assess the adhesive performance of resin-based biomaterials included shear bond strength tests, tensile and microtensile bond strength tests, pushout bond strength tests, microleakage assessments using dye penetration, analysis of marginal adaptation using X-ray microtomography, and marginal gap measurements.

3.2.6. Effects of Irradiation on Bond Strength

In seven studies that assessed bond strength on flat, ground enamel and/or dentin specimens, irradiation reduced the bond strength of dental adhesives and resin-based composite [30,33,34,37–40]. In one study, irradiation reduced the bond strength on dentin but not enamel [29]. No significant difference between irradiated and unirradiated specimens was found in three studies [32,41,42]. Two studies found that irradiation impaired the bond strength of some adhesives but not others [31,43].

Different adhesives obtained significantly different bond strength in six studies [30,31,31,34,42,43]. The enamel bond strength of a universal adhesive was higher when applied in etch-and-rinse mode compared with self-etch mode [41].

Irradiation decreased the push-out bond strength of endodontic quartz fiber posts, with the most pronounced drop in bond strength occurring in specimens subjected to irradiation prior to the adhesive luting procedure [44].

A decrease in enamel bond strength of orthodontic brackets was observed in three of four studies that compared irradiated enamel specimens with unirradiated specimens [45–47]. No significant decline in enamel bond strength of orthodontic brackets was found in one study [36].

The timing of irradiation in relation to the restorative procedure was found to have a significant impact on adhesive performance in all included studies that assessed this parameter [30,37–39,43,44]. According to three studies, the most pronounced detrimental impact was found in specimens subjected to irradiation before the restorative procedure [37,38,44]. One study found that the impact of the timing of irradiation differed depending on the type of adhesive used [43].

Both studies that evaluated dose–effect relationships reported a dose-dependent decrease in dentin bond strength [29,33]. In one of these studies, a similar exposure–effect relationship was also observed on enamel [33], while the other study did not find any such relationship [29].

3.2.7. Effects of Irradiation on Microleakage

In three of four studies that evaluated microleakage, a higher degree of microleakage occurred in irradiated specimens than in unirradiated ones [28,35,48]. Lower degrees of microleakage were detected in teeth that had been covered with aluminum shields during irradiation [35]. No significant difference in microleakage between irradiated and unirradiated specimens was found in one study [49]. Specimens bonded with an etch-and-rinse adhesive showed more microleakage at the cervical dentin margin than specimens bonded with self-etch adhesives [49].

3.2.8. Effects of Irradiation on Marginal Adaptation

The three included studies that assessed the marginal adaptation of direct resin-based composite restorations reported conflicting findings. Irradiation did not significantly affect the marginal adaptation of direct resin-based composite restorations bonded with a universal adhesive in one investigation [18]. In specimens subjected to irradiation before the restorative procedure, more marginal defects were observed in restorations bonded with a universal adhesive applied in self-etch mode compared with the same adhesive in etch-and-rinse mode [18]. One study found that the marginal gap of direct resin-based composite restorations was higher in irradiated than unirradiated specimens [40].

3.3. Risk of Bias

Table A2 reports in detail the results of the RoBDEMAT assessments of the included studies. The signaling questions of the RoBDEMAT tool are provided in the Supplementary Materials. Randomization of samples, sample size rationale and reporting, and blinding of test operators were the domains where the RoBDEMAT assessments most frequently indicated insufficient reporting, methodological limitations, or both.

4. Discussion

This systematic review provided a critical appraisal of 23 laboratory studies assessing the effects of irradiation, performed to simulate head and neck cancer treatment, on bond strength, microleakage, and marginal adaptation of dental restorations made with resin-based biomaterials. Irradiation reduced the bond strength of dental adhesives and resin-based composites on flat, ground enamel and/or dentin specimens in most studies. Different adhesives and timing of irradiation had a significant impact on adhesive performance. Irradiation also increased microleakage in most studies. The effect of irradiation on marginal adaptation of direct resin-based composite restorations was inconclusive, with conflicting findings reported in the included studies.

Although this systematic review offers valuable insights into the effects of irradiation on adhesive performance of resin-based biomaterials, it is important to consider its limitations. The review was confined to laboratory studies that evaluated resin-based biomaterials, which limits the scope of its findings. Glass ionomer cements can release fluoride and act as refillable fluoride reservoir, potentially curbing the development of secondary caries, especially in high-risk patients undergoing radiation therapy [10]. However, it remains unclear which biomaterial is most suitable for treating radiation-related caries based on available clinical evidence [10]. This paucity of evidence underscores the need for further laboratory and clinical investigations that evaluate the performance of different biomaterials and explore methods for improving their effectiveness.

The risk-of-bias assessment of the included studies revealed some opportunities for improvement in methodological design and reporting, particularly in the areas of sample randomization, sample size justification and reporting, and blinding of investigators. To assist researchers in designing laboratory studies that assess dental materials and in drafting study reports, the RoBDEMAT checklist, along with reporting guidelines issued by the Equator Network (www.equator-network.org [accessed on 23 March 2023]), can be a useful tool [23].

Irradiation causes a degradation of the interprismatic substance of enamel [50]. There is also a decrease in crystallinity of hydroxyapatite and an increase in the protein-to mineral ratio [12]. As a result, achieving strong and stable bonding to irradiated enamel is more challenging compared to unirradiated enamel. Most of the studies on enamel bonding reported that irradiation reduces the bond strength. However, a few studies found no significant impact of irradiation on bond strength, including one that investigated the bonding of resin-modified glass ionomer cement [29,36,41]. The reduced bond strength observed in most studies is likely due to the microstructural changes in enamel caused by irradiation, which can make it more difficult for adhesives to bond effectively.

The effect of irradiation on dentin appears to be more severe than enamel owing to the higher content of water and organic matter. In dentin, decarboxylation caused by irradiation destroys the electrostatic linkages between the carboxylate and phosphate side-chains of collagen and leads to a decoupling of calcium from collagen side-chains [14,50]. These disruptions in collagen and obliteration of dentinal tubules may compromise the dentin bond by impairing the hybrid layer [30,41]. This effect is evidenced by the reduction in or loss of resin tags and thin hybrid layers reported for bonding to irradiated dentin [30]. However, one-half of the studies that investigated tensile bond strength to dentin reported that irradiation reduced bond strength, while the other half found no difference. For studies that investigated shear bond strength, a majority—seven out of nine studies—reported that irradiation led to a decrease in bond strength. However, one study using deciduous molars reported that a 6 month delay in bonding after irradiation improves the bond strength, suggesting that there may be some recovery of the damage over time [30].

In line with the body of published evidence, etch-and-rinse adhesives appear to provide higher bond strengths to both irradiated and control enamel than self-etch adhesives applied without prior phosphoric acid etching [21,33,51]. Interestingly, studies that investigated shear bond strength reported that self-etch adhesives provided higher bond strength to dentin [30,34]. In contrast, one study assessing microtensile bond strength reported that the tested etch-and-rinse adhesive achieved better bond strength than the self-etch adhesive on dentin [27]. These differences in findings may be due to variations in stress distribution at the test interface for the two modalities [52]. Additionally, consistent with strong evidence derived from clinical and laboratory studies, the findings of this systematic review indicate a significant difference in adhesive performance of different adhesives [20,21].

Assessments of microleakage can be used to evaluate the adhesive performance and quality of restorations. Four studies investigated microleakage of restorations placed in irradiated teeth. The majority of these studies reported higher microleakage in irradiated teeth compared with control teeth [28,35,48]. However, one study found no difference in leakage between irradiated and unirradiated teeth and reported better results with a self-etch adhesive than an etch-and-rinse adhesive at cervical margins of restorations [49]. Additionally, one study that evaluated marginal adaptation of irradiated teeth using X-ray microtomography found no difference in adaptation but more dentin margin defects in specimens bonded with a self-etch adhesive [18].

Conventional fractionation radiation therapy with a total dose level of 60 to 66 Gy is a standard of care in high-risk patients with squamous-cell carcinoma of the head and neck [4,5]. Most of the laboratory studies included in this review simulated this by subjecting specimens to a total dose of 60 Gy. However, the dosage of radiation that reaches tooth structure during radiation treatment can vary depending on tumor location and size, as well as the efficiency of targeting of radiation. Oral stents and lead shielding can be used to reduce radiation to surrounding tissues during radiation treatment [50]. Advances in the use of intensity-modulated radiation therapy are also expected to reduce damage to surrounding tissues [53]. One study evaluated the use of lead shielding to simulate the attenuation of radiation to teeth and reported that shielding reduced the microleakage of restorations [35]. As it is possible to place protective appliances on teeth or the entire dental arch, it is worth exploring approaches to minimize the harmful effects of radiation by utilizing such intraoral shielding devices. Further investigation in this area is warranted to determine the most effective methods for reducing radiation damage to dental structures.

According to the findings of this systematic review, patients with head and neck cancer who are scheduled to undergo radiation treatment should receive dental evaluation and necessary restorative treatments before radiation therapy begins. To minimize radiation exposure of teeth, measures such as lead shielding and stents should be used whenever possible. Given that bond strength of restorations that are placed 6 months after radiation may equal that of unirradiated teeth, restorations placed 6 months or longer after radiation therapy may obtain better adhesive performance compared with restorations placed within half a year of radiation therapy. While it is advantageous to use enamel conditioning with phosphoric acid, there is no consensus on the preferred adhesive strategy for bonding to irradiated dentin. Dental practitioners need to consider the difference in performance of different adhesives and select restorative materials with due care.

5. Conclusions

This systematic review generated several important conclusions that are relevant to both research and clinical patient care.

- Evidence derived from laboratory studies suggests that irradiation has a detrimental effect on the adhesive performance of resin-based dental biomaterials.
- The long-term impact of radiation on dental adhesion remains unclear, but it is plausible that the adverse effects may lessen with time between radiation therapy and the restorative procedure. However, current evidence on this is scanty.
- Significant differences have been observed in the performance of different adhesives on irradiated enamel and dentin. To achieve favorable restorative outcomes, it is, therefore, crucial to choose adhesives with a proven performance record in both laboratory and clinical studies, and to take painstaking care during bonding and buildup procedures.
- Further research is necessary to gain a comprehensive understanding of the effects of irradiation on teeth with restorations, develop methods to mitigate the adverse effects of irradiation, and explore ways to improve the efficacy of dental restorations.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/ma16072580/s1: Table S1. Search strings used for the searches in five electronic databases; Table S2. RoBDEMAT tool used to assess the risk of bias of included studies.

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Appendix A

Table A1. Overview of the main characteristics of laboratory studies included in the systematic review.

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Aggarwal et al., 2009 [44]	Human mandibular premolars	60 in total (15 per group)	Quartz fiber posts bonded with an E&R adhesive and dual curing RBLM in root canal treated teeth	Root canal-treated teeth	Four groups (no irradiation, irradiation before restoration, restoration during irradiation, restoration after irradiation)	6 weeks with daily irradiation to a total dose of 60 Gy	E&R adhesive (All Bond 2 Bisco, Schaumburg, IL, USA); dual-curing RBLM (Duolink, Bisco, Schaumburg, IL, USA) RBC build-up (Light-Core Composite resin core material, Bisco, Schaumburg, IL, USA)	Push-out bond strength	Irradiation decreased bond strength to root dentin. The timepoint of irradiation had a significant impact on bond strength, with the most detrimental effect occurring in specimens that underwent irradiation prior to restorative treatment.
Anushree et al., 2021 [45]	Human enamel from premolars	66 in total (22 per group)	Metallic orthodontic brackets bonded to enamel (with or without subsequent thermocycling)	Premolars embedded in acrylic	3 groups (unirradiated without thermocycling, unirradiated with thermocycling, irradiated with thermocycling)	2 Gy per day for 5 consecutive days per week over 6 weeks (total dose of 60 Gy) after the bonding procedure	E&R adhesive (Transbond XT, 3M, St. Paul, MN, USA)	Shear bond strength assessment	Significant decrease in shear bond strength in irradiated specimens compared with unirradiated specimens.
Arid et al., 2020 [34]	Human enamel and dentin	120 enamel and 120 dentin specimens made from 60 third molars (15 specimens per group)	Flat, ground enamel and dentin surfaces	Standardized RBC restorations (3 separate increments)	4 groups (no irradiation, restoration immediately before irradiation, restoration immediately after irradiation, restoration 6 months after irradiation); 2 subgroups (E&R adhesive vs. SE adhesive)	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	E&R adhesive (Adper Single Bond 2, 3M, St. Paul, MN, USA); SE adhesive (Clearfil SE Bond, Kuraray, Okayama, Japan)	Shear bond strength assessment	Irradiation changed the morphological surface of enamel and dentin and reduced the bond strength. The SE adhesive produced higher bond strength than the E&R adhesive. Restoration before irradiation resulted in the lowest bond strength on enamel and dentin.

Table A1. *Cont.*

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Bulucu et al., 2006 [43]	Human dentin from molars	30 teeth in total (six subgroups, each with 10 teeth)	Flat, ground dentin surfaces	Standardized restorations made with direct RBC	3 main groups (no irradiation, irradiation before restoration, irradiation after restoration); two subgroups (two different adhesives)	2 Gy per day for 5 consecutive days per week over 6 weeks (total dose of 60 Gy) before or after the bonding procedure	Two-step SE adhesive (Clearfil SE Bond, Kuraray, Japan); E&R adhesive (Prime & Bond NT, Dentsply, Milford, DE, USA); RBC (Clearfil ST, Kuraray, Okayama, Japan)	Shear bond strength assessment	Depending on the adhesive, irradiation before or after the restorative procedure can decrease bond strength.
Mellara et al., 2020 [30]	Human deciduous molars	120 enamel and 120 dentin specimens made from 60 deciduous molars (4 subgroups each with 30 enamel and 30 dentin specimens)	Flat enamel and dentin surfaces	Standardized RBC restorations (RBC applied in increments)	Four groups (no irradiation, restoration immediately before irradiation, restoration 24 h after irradiation, restoration 6 months after irradiation)	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	E&R adhesive (Adper Single Bond 2, 3M, St. Paul, MN, USA); SE adhesive (Clearfil SE Bond, Kuraray, Okayama, Japan)	Shear bond strength assessment	The restorations placed immediately after irradiation had the lowest shear bond strength, and the restorations placed 6 months after irradiation had similar bond strength compared with the unirradiated teeth in enamel, regardless of the adhesive system used. In dentin, the SE adhesive performed better performance than the E&R adhesive.

Table A1. *Cont.*

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Muñoz et al., 2020 [33]	Human enamel and dentin	52 third molars, 40 teeth used for bond strength testing (8 subgroups each with 5 specimens)	Flat, ground dentin surfaces	Standardized restorations made with direct RBC	4 main groups (no irradiation, irradiation with 20 Gy, 40 Gy, or 70 Gy before restoration); 2 subgroups (universal adhesive applied in E&R mode vs. SE mode)	Total doses of 0 Gy, 20 Gy, 40 Gy, or 70 Gy	Universal adhesive (Scotchbond Universal Adhesive, 3M, St. Paul, MN, USA)	Shear bond strength assessment	On enamel and dentin, irradiation with ≥40 Gy decreased bond strength regardless of the adhesive strategy. The universal adhesive applied in E&R mode showed a better adhesive performance compared with the SE mode.
Neto et al., 2022 [46]	Human enamel	60 human premolars	Flat enamel surface	Orthodontic brackets bonded to flat enamel surface	4 groups with 15 teeth each (no irradiation vs. irradiation before bonding procedure; Transbond XT vs. Light Bond)	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	E&R adhesives (Transbond XT Primer, 3M, St. Paul, MN, USA), E&R adhesive (Light Bond, Reliance Orthodontic Products, Itasca, IL, USA); RBC (Transbond XT, 3M, Monrovia, CA, USA); RBC (Light Bond, Reliance Orthodontic Products, Itasca, IL, USA)	Shear bond strength assessment	Irradiation impaired the adhesion of ceramic brackets, regardless of the RBC used for bonding.

Table A1. *Cont.*

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Oglakci et al., 2022 [41]	Human enamel and dentin	90 enamel and 90 dentin specimens made from 90 human molars (12 subgroups, each with 15 specimens)	Polished enamel and dentin surfaces on whole teeth	Flattened lingual and buccal surfaces of molar teeth	Enamel (control, restoration before irradiation, restoration after irradiation); dentin (control, restoration before irradiation, restoration after irradiation); adhesive applied in E&R or SE mode	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	Universal adhesive (Clearfil Universal Bond Quick, Kuraray, Okayama, Japan); RBC (Estelite Posterior Quick, Tokuyama Dental, Tokyo, Japan)	Shear bond strength assessment	On enamel, the bond strength of the universal adhesive was higher in the E&R mode and the SE mode. On dentin, the universal adhesive achieved similar bond strength in E&R and SE mode. Irradiation and the timing of the restorative procedure had no significant impact on the adhesive performance on enamel and dentin.
Santin et al., 2018 [36]	Human enamel from premolars	90 teeth (6 groups with 15 specimens each)	Flat enamel surface	Orthodontic brackets bonded to flat enamel surface	Two main groups (irradiation before bonding vs. no irradiation); three subgroups (RBC, GIC, RMGIC)	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	E&R adhesive (XT Primer,3M, St. Paul, MN, USA); RBC (Transbond XT, 3M, St. Paul, MN, USA); RMGIC (Fuji Ortho LC resin, GC, Tokyo, Japan)	Shear bond strength assessment	Irradiation had no significant impact on the adhesion of brackets bonded with RBC and RMGIC. RBC and RMGIC achieved higher bond strength than GIC.
Santin et al., 2015 [47]	Human molars and premolars	10 human molars and 90 human premolars (six subgroups with 15 specimens each)	Polished buccal enamel surfaces	Metallic and ceramic orthodontic brackets bonded to enamel	2 main groups (metal and ceramic brackets bonded to enamel). Three subgroups (no irradiation, no irradiation, thermocycling after bonding; irradiation before bonding and thermocycling after bonding)	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	E&R adhesive (XT Primer, 3M, St. Paul, MN, USA); RBC (Transbond XT, 3M, St. Paul, MN, USA)	Shear bond strength assessment	Irradiation decreased enamel bond strength.

Table A1. *Cont.*

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Tikku et al., 2023 [40]	Human dentin	100 molars (10 subgroups each with 10 teeth)	Flat, ground dentin surfaces	Standardized restorations made with direct RBC (separate, 2.5 mm thick increments)	Two main groups (irradiation after bonding vs. no irradiation); five subgroups (three different RBCs and two different GICs)	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	E&R adhesive (Adper Single Bond Plus, 3M, St. Paul, MN, USA); RBC (Filtek Z250, 3M, St. Paul, MN, USA), RBC (Filtek Z350XT, 3M, St. Paul, MN, USA, RBC (Filtek Bulk Fill, 3M, St. Paul, MN, USA)	Shear bond strength assessment; marginal gap assessment	Regardless of the material, lower bond strength and larger marginal gaps were observed in specimens subjected to irradiation.
Bernard et al., 2015 [31]	Human dentin	40 teeth total (10 per group)	Direct Class I restorations on molars; direct Class V restorations on premolars canines, and incisors	1 mm^2 sticks	2 main groups (irradiated vs. unirradiated teeth) 2 subgroups (a three-step E&R adhesive vs. a two-step SE adhesive	In vivo irradiation with total dose of $\geq$50 Gy	Three-step E&R adhesive (Optibond FL, Kerr, Creteil, France); Two-step SE adhesive (Optibond XTR, Kerr, Creteil, France); RBC (Herculite XRV Ultra, Kerr, Creteil, France)	Microtensile bond strength	The SE adhesive achieved similar bond strength in irradiated and unirradiated teeth. The E&R adhesive achieved higher bond strengths on unirradiated than on irradiated teeth. Restorative treatment should ideally be performed before radiation therapy.
Galetti et al., 2014 [32]	Human dentin	18 teeth from patients who underwent radiation therapy and 18 teeth form patients without radiation therapy (divided into six subgroups, each with 6 specimens)	Flat, ground dentin surfaces	Standardized restorations made with direct RBC	Two main groups (irradiated teeth vs. unirradiated teeth); three subgroups (three different adhesives)	Clinical radiation therapy prior to tooth removal (total dose 60–70 Gy)	E&R adhesive (Single Bond 2, 3M, St. Paul, MN, USA); two step SE adhesives (Easy Bond, 3M, St. Paul, MN, USA), SE adhesive (Clearfil SE Bond, Kuraray, Okayama, Japan)	Microtensile bond strength assessment	No significant difference was observed between irradiated and unirradiated teeth. The adhesives obtained similar bond strength.

Table A1. *Cont.*

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Gernhardt et al., 2001 [42]	Human third molars	120 teeth in total (60 with and 60 without irradiation) 4 subgroups, each with 15 specimens	Occlusal surface ground to expose dentin With simulated intra-pulpal pressure	Flat, ground dentin surfaces	2 main groups (irradiated vs. unirradiated) 4 subgroups (4 different adhesives)	5 days/week to a total dose of 60 Gy	Universal Adhesive (Scotchbond 1, 3M, Loughborough, UK); Universal Adhesive (Solobond Plus, Voco, Cuxhaven, Germany); 2-step E&R adhesive (Prime & Bond 2.1, DeTrey Dentsply, Dreieich, Germany); 4-step total etch adhesive (Syntac, Vivadent, Schaan, Liechtenstein); RBC (Tetric, Vivadent, Schaan, Lichtenstein)	Tensile bond strength	Irradiation had no significant influence on adhesion of RBC to dentin. On irradiated dentin, Scotchbond 1 obtained higher bond strength than Solobond Plus, and Prime & Bond obtained higher bond strength than Solobond Plus.
Keles et al., 2018 [29]	Enamel and dentin from deciduous human molars	35 deciduous molars (7 subgroups with 5 specimens each)	Flat enamel and dentin surfaces	Standardized compomer restorations (3 separate increments, each 2 mm thick)	Six groups (no irradiation, 10 Gy, 20 Gy, 30 Gy, 40 Gy, 50 Gy, or 60 Gy before restorative procedure)	2 Gy daily for 5 days per week over a maximum of 6 weeks (total dose 10–60 Gy)	SE adhesive (Futurabond M, Voco, Cuxhaven, Germany); compomer restorative resin-based material (Glossiosit, Voco, Cuxhaven, Germany	Microtensile bond strength assessment	No statistically significant difference was found between the irradiated tooth enamel and the control group. A dose-dependent decrease in bond strength was found on dentin of deciduous molars.

Table A1. *Cont.*

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Naves et al., 2012 [37]	Human enamel and dentin	120 specimens made from 30 third molars (40 specimens per group)	Flat, ground enamel and dentin surfaces	Standardized RBC restorations (3 separate increments)	Enamel and dentin specimens without irradiation; enamel and dentin specimens with irradiation before restoration; enamel and dentin specimens with irradiation after restoration	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	E&R adhesive (Adper Single Bond 2, 3M, St, Paul, MN, USA); RBC (Filtek Z250, 3M, St. Paul, MN, USA)	Microtensile bond strength assessment	Irradiation reduced bond strength to human enamel and dentin when the adhesive procedure was performed after irradiation. When the adhesive procedure was performed before irradiation, no significant change in bond strength was observed.
Rodrigues et al., 2018 [38]	Dentin from human third molars	43 specimens (depending on the type of assessment, the subgroups comprised 1–10 specimens)	Standardized sections of dentin	Standardized restorations made with direct RBC (separate increments)	Three groups (no irradiation, irradiation before restoration, irradiation after restoration)	1.8 Gy daily, 5 days per week, for 8 weeks (total dose 72 Gy)	E&R adhesive (Scotchbond Multi-Purpose, 3M, St. Paul, MN, USA); RBC (Filtek Z350 XT, 3M, St. Paul, MN, USA)	Microtensile bond strength assessment	In the group with irradiation before the restorative procedure, significantly lower bond strengths were observed compared with the other groups.
Soares et al., 2016 [39]	Human dentin	60 human molars (12 subgroups with 5 specimens each)	Flat, ground dentin surfaces	Standardized restorations made with direct RBC (separate, 2.0 mm thick increments)	Three main groups (no irradiation, irradiation before restoration, irradiation after restoration); four subgroups (two different adhesives with and without prior application of doxycycline)	2 Gy daily for 5 days per week over six weeks (total dose 60 Gy)	E&R adhesive (Adper Scotchbond Multi-Purpose, 3M, St. Paul, MN, USA); SE adhesive (Clearfil SE Bond, Kuraray, Okayama, Japan); RBC (Filtek Z250, 3M, St. Paul, MN, USA)	Microtensile bond strength assessment	Irradiation before the adhesive procedure decreased bond strength. No statistical difference was observed between the adhesive systems.

Table A1. *Cont.*

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Bulucu et al., 2009 [49]	Human enamel and dentin from molars	84 teeth in total (six subgroups, each with 14 teeth)	Direct Class V restorations in molars (cavities margins in enamel and dentin)	Box-shaped Class V cavities and direct restorations	2 main groups (irradiation after restoration vs. no irradiation), three subgroups (three different adhesives)	2 Gy per day for 5 consecutive days per week over 6 weeks (total dose of 60 Gy) after the bonding procedure	One-step SE adhesive (Clearfil S3 Bond, 3M, St. Paul, MN, USA); a two-step SE adhesive (Clearfil SE Bond, 3M, St. Paul, MN, USA); a E&R adhesive (Prime & Bond NT, Dentsply, Milford, DE, USA); RBC (Filtek Z250, 3M, St. Paul, MN, USA)	Microleakage assessment using dye penetration	No statistically significant differences in microleakage were found between irradiated and unirradiated specimens. Specimens bonded with SE adhesives showed less microleakage at cervical margins than the E&R adhesive.
Gupta et al., 2022 [35]	Human premolars	75 teeth (5 groups with 15 teeth each)	Direct Class V restorations on buccal surfaces; thermocycling; preparation of sections	Direct Class V restorations on buccal surfaces	5 groups (no irradiation; irradiation before restoration; irradiation with shielding before restoration; irradiation after restoration; irradiation with shielding after restoration)	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	SE adhesive (Adper Easy 1, 3M, St. Paul, MN, USA); RBC (Valux Plus, 3M, St. Paul, MN, USA))	Microleakage assessment using dye penetration	Irradiation increased microleakage. Microleakage was higher if restorations were placed after irradiation. Shielding reduced microleakage. Restorations should ideally be placed before irradiation.
Jornet et al., 2013 [28]	Bovine incisors	60 teeth in total (6 groups with 10 specimens each)	Direct RBC restorations	Class V restorations in anterior teeth	2 main groups (irradiated after restoration vs. unirradiated specimens) 3 subgroups (storage in artificial saliva, fluoride solution, or chlorhexidine)	2 Gy daily for 5 days per week over 6 weeks (total dose 60 Gy)	Universal adhesive (Single Bond, 3M, St. Paul, MN, USA); RBC (Z250, 3M St. Paul, MN, USA)	Microleakage assessment using methylene blue penetration	Irradiated teeth showed more microleakage. Irradiated teeth immersed in chlorhexidine showed the highest leakage. Among irradiated teeth, those immersed in fluoride solution showed the lowest leakage.

Table A1. *Cont.*

Study	Dental Specimens (Enamel, Dentin, or Both; Human, Bovine, or Both)	Number of Specimens	Specimen Fabrication	Specimen Shape	Sample Grouping	Irradiation Protocol	Adhesives and Resin-Based Materials Used	Test Method(s) Used to Assess Adhesive Performance	Main Findings
Rasmy et al., 2017 [48]	Human enamel and dentin	40 teeth, 80 specimens of buccal and lingual segments (20 specimens per group)	Class V restorations	Standardized Class V restorations made with direct RBC	Two main groups (irradiation before bonding vs. no irradiation); two subgroups (enamel conditioning with laser vs. phosphoric acid)	60 Gy	E&R adhesive (Adper Single Bond, 3M, St. Paul, MN, USA); RBC (Filtek Z 250, 3M, St. Paul, MN, USA)	Microleakage assessment	Favorable results were found in specimens without irradiation. Regardless of the surface conditioning, a high degree of microleakage was found in specimens with irradiation.
Oglakci et al., 2022b [18]	Human molars	60 in total (six subgroups, each with 10 specimens)	MOD restorations evaluated at the enamel and dentin margins	Molar teeth with MOD restorations	3 main groups (no irradiation; irradiation before restoration; irradiation after restoration); 2 subgroups (universal adhesive applied in E&R or SE mode)	60 Gy at 2 Gy/day, 5 days a week for 6 weeks	Universal adhesive (Clearfil Universal Bond Quick, Kuraray, Okayama, Japan); RBC (Estelite Posterior Quick, Tokuyama Dental, Tokyo, Japan)	Analysis of marginal adaptation done using X-ray microtomography	Irradiation did not affect the marginal adaptation of the universal adhesive at the cervical regions. In specimens subjected to irradiation before the restorative procedure, more adhesive defects at the dentin margin were observed in the SE group than in the E&R group.

E&R, etch-and-rinse; *GIC*, glass ionomer cement; *Gy*, gray; *RBC*, resin-based composite; *RBLM*, resin-based luting material; *RMGIC*, resin-modified glass ionomer cement; *SE*, self-etch.

Table A2. Results of the risk of bias assessment. Each RoBDEMAT signaling question in the four domains, D1, D2, D3, and D4, was answered as "sufficiently reported/adequate" (1), "insufficiently reported" (2), "not reported/not adequate" (3), or "not applicable" (4) [23].

	D1			D2		D3		D4	
Study	**(1.1) Control Group**	**(1.2) Randomization of Samples**	**(1.3) Sample Size Rationale and Reporting**	**(2.1) Standardization of Samples and Materials**	**(2.2) Identical Experimental Conditions Across Groups**	**(3.1) Adequate and Standardized Testing Procedures and Outcomes**	**(3.2) Blinding of the Test Operator**	**(4.1) Statistical Analysis**	**(4.2) Reporting Study Outcomes**
Aggarwal et al., 2009 [44]	1	3	3	1	1	1	3	1	1
Anushree et al., 2021 [45]	1	2	1	1	1	1	3	1	1
Arid et al., 2020 [34]	1	1	3	1	1	1	1	1	1
Bernard et al., 2015 [31]	1	2	2	1	1	1	3	1	1
Bulucu et al., 2006 [43]	1	2	3	1	1	1	3	1	1
Bulucu et al., 2009 [49]	1	2	3	1	1	1	3	1	1
Galetti et al., (2014) [32]	1	2	3	3	1	1	3	1	1
Gernhardt et al., 2001 [42]	1	2	3	1	1	1	3	1	1
Gupta et al., 2022 [35]	1	2	3	1	1	1	3	1	1
Jornet et al., 2013 [28]	1	1	1	1	1	1	1	1	1
Keles et al., 2018 [29]	1	2	3	1	1	1	3	1	1
Mellara et al., 2020 [30]	1	2	3	1	1	1	1	1	1
Muñoz et al., 2020 [33]	1	1	3	1	1	1	3	1	1
Naves et al., 2012 [37]	1	2	3	1	1	1	3	1	1
Neto et al., 2022 [46]	1	2	1	1	1	1	3	1	1
Oglakci et al., 2022 [41]	1	2	1	1	1	1	1	1	1
Oglakci et al., 2022 [18]	1	1	1	1	1	1	1	1	1
Rasmy et al., 2017 [48]	1	3	3	1	1	2	1	1	1
Rodrigues et al., 2018 [38]	1	2	3	1	1	2	3	1	1
Santin et al., 2018 [36]	1	2	3	1	1	1	3	1	1
Santin et al., 2015 [47]	1	3	3	1	2	1	3	2	2
Soares et al., 2016 [39]	1	2	3	1	1	1	3	1	1
Tikku et al., 2023 [40]	1	2	3	1	1	1	3	1	1

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